

In the Abstract

Please substitute the following amended Abstract for the abstract as currently pending.

A3  
Polymeric crosslinking agents are disclosed that have an inert water soluble polymeric component, biodegradable components, functional components reactive with chemical groups on a protein, for example, amine or thiol groups. The inert polymeric component may be flanked at each end with a biodegradable component which is flanked at each end with a protein reactive functional component. A polymeric crosslinking agent is disclosed having a biodegradable component, polyalkylene oxide, and at least three reactive functional groups that are each capable of forming a covalent bond in water with at least one functional group such as an amine, thiol, or carboxylic acid.

REMARKS

Claims 1-22 are pending. By this Amendment, claims 1-22 are canceled and new claims 23-48 are added.

In view of the foregoing, it is submitted that this application is in condition for allowance. Favorable consideration and prompt allowance of the application are respectfully requested.

The Examiner is invited to telephone the undersigned if the Examiner believes it would be useful to advance prosecution.

Respectfully submitted,



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ATTACHMENT  
REDLINED AMENDMENT

Title as Amended

Please substitute the following amended title for the title as currently on record.

CROSSLINKING AGENTS AND METHODS OF USE

In the Specification

Please substitute the following amended paragraph :

Page 1, lines 5-8, This application is a divisional of U.S. application serial no. 09/147,897 filed August 30, 1999 entitled "Methods and Devices for Preparing Protein Concentrates" filed under 35 U.S.C. §3.71 with priority to International Application No. PCT/US97/16897, which claims priority to U.S. application serial no. 60/026,536 filed September 23, 1996; U.S. application serial no. 60/039,904 filed March 4, 1997 and U.S. application serial no. 60/040,417 filed March 13, 1997, the disclosures of which are herein incorporated by reference.

Page 1, line 12, The field of the invention is synthetic and natural molecules used to make polymers for treating patients.

Claims As Amended

Please cancel claims 1-22 without prejudice or disclaimer.

Please add new claims 23-48 as follows:

23. (New) A water soluble polymeric crosslinking agent comprising:
- an inert polymeric component,
  - a biodegradable component, and
  - a protein reactive functional component.
24. (New) The crosslinking agent of claim 23 wherein said crosslinking agent is linear.

25. (New) The crosslinking agent of claim 23 wherein said crosslinking agent comprises a plurality of branches, wherein said plurality is greater than two.

26. (New) The crosslinking agent of claim 23, wherein said inert polymeric component is flanked at each end with said biodegradable component which is flanked at each end with said protein reactive functional component.

27. (New) The crosslinking agent of claim 26, wherein the protein reactive functional component is chosen from the group consisting of carbodiimidazole, sulfonyl chloride, chlorocarbonates, hydroxysuccinimidyl esters, aryl halides, sulfasuccinimidyl esters, and maleimides.

28. (New) A polymeric crosslinking agent for use in vivo with a patient comprising a biologically inert core attached to a polymer having a biodegradable component with the polymer being attached to a reactive functional group capable of forming a covalent bond in water with at least one functional group chosen from the group consisting of amine and thiol, wherein the crosslinking agent has at least two functional groups and is water soluble.

29. (New) The crosslinking agent of claim 28 wherein the biodegradable component does not contain amino acids assembled in amino acid sequences that are enzymatically degradable when the crosslinker is placed in a patient.

30. (New) The crosslinking agent of claim 28 wherein the biodegradable component comprises a polymer chosen from the group consisting of glycolide, lactide, caprolactone, dioxanone, and trimethylene carbonate.

31. (New) The crosslinking agent of claim 28 wherein the biodegradable component comprises a hydrolytically degradable chemical group chosen from the group consisting of ester, acetal, anhydride, orthoester, or disulfide.

32. (New) The crosslinking agent of claim 28 wherein the biodegradable component comprises a polymer chosen from the group consisting of polyhydroxyacid, polyorthocarbonate, polyanhydride, polylactone, polyaminoacid, and polyphosphate.

33. (New) The crosslinking agent of claim 28 wherein the biodegradable component is hydrolyzable under in vivo conditions.

34. (New) A polymeric crosslinking agent for use in vivo with a patient comprising a biologically inert core attached to two branches that each comprise a biodegradable component hydrolyzable under in vivo conditions and are terminated with a reactive end group capable of forming a covalent bond in water with at least one functional group chosen from the group consisting of amine and thiol wherein 1 g of the crosslinking agent is soluble in 100 milliliters of water.

35. (New) The crosslinking agent of claim 34 having at least four of the branches.

36. (New) The crosslinking agent of claim 34 wherein the biodegradable polymer comprises a polymer chosen from the group consisting of glycolide, lactide, caprolactone, dioxanone, and trimethylene carbonate.

37. (New) The crosslinking agent of claim 34 wherein the biodegradable polymer comprises a polymer chosen from a group consisting of polyhydroxyacid, polyorthocarbonate, polyanhydride, polylactone, polyaminoacid, and polyphosphate.

38. (New) The crosslinking agent of claim 34 wherein the core comprises polyalkylene oxide.

39. (New) The crosslinking agent of claim 38 wherein the core comprises at least three sequential  $-(CH_2CH_2O)-$  repeats.

40. (New) The crosslinking agent of claim 34 having a molecular weight from 600 to 10,000.

41. (New) The crosslinking agent of claim 34 having a molecular weight from 600 to 100,000.

42. (New) A method of making a polymeric crosslinking agent for use in vivo with a patient comprising activating at least two end groups of a polymer that comprises a biodegradable component hydrolyzable under in vivo conditions and polyalkylene oxide such that the polymer is thereby terminated with reactive functional groups that are capable of forming a covalent bond in water with at least one functional group chosen from the group consisting of amine and thiol.

43. (New) The method of claim 42 comprising choosing the biodegradable component to comprise a member of the group consisting of glycolide, lactide, caprolactone, dioxanone, and trimethylene carbonate.

44. (New) The crosslinking agent made according to the process of claim 43.

45. (New) The method of claim 42 comprising choosing the biodegradable component to comprise a member of the group consisting of polyhydroxyacid, polyorthocarbonate, polyanhydride, polylactone, polyaminoacid, and polyphosphate.

46. (New) The crosslinking agent made according to the process of claim 45.

47. (New) The method of claim 42 comprising making the crosslinking agent to have a molecular weight from 600 to 10,000.

48. (New) The crosslinking agent of claim 42 having a molecular weight from 600 to 100,000.

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